Drug News
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Issue Number 82

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in August 2016 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).

Safety Update

UK: Class 4 Medicines Defect Information (Caution in Use): Actilyse 20mg and 50mg powder and solvent for solution for injection and infusion (alteplase)

On 24 August 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a Class 4 Drug Alert for Actilyse 20mg and 50mg powder and solvent for solution for injection and infusion (alteplase).

Boehringer Ingelheim Limited has received an increased number of complaints relating to the rubber stoppers being pushed into the vial during reconstitution using the supplied transfer cannula. This renders the vial unusable. Boehringer Ingelheim Limited have provided guidance to Healthcare Professionals on the handling of the transfer cannula.

In Hong Kong, Actilyse Lyophilised Pdr for IV Inf 50mg (HK-30511) and Actilyse Lyophilised Pdr for IV Inj 20mg (HK-37894) are pharmaceutical products registered by Boehringer Ingelheim (HK) Ltd (BI), and are prescription only medicines. As on 1 November 2016, the Department of Health (DH) has not received any adverse drug reaction (ADR) report related to the products. According to BI, only Actilyse 50mg is marketed in Hong Kong and is sold to hospitals, while Actilyse 20mg has not been marketed. On 26 August 2016, BI has disseminated letters to hospital pharmacies regarding the issue, together with handling instructions of the transfer set. DH will remain vigilant on the safety of the products and any further update from BI.

Canada: REVOLADE (eltrombopag) - Risk of Severe Hepatotoxicity

On 25 August 2016, Health Canada reported that a recent review of all clinical trial and post-marketing cases identified five (5) cases fulfilling Hy's law criteria (severe drug-induced liver injury).

REVOLADE (eltrombopag) tablets are indicated in Canada:

- For adult chronic immune thrombocytopenia purpura (cITP) to increase platelet counts in splenectomized patients who are refractory to first-line treatments (e.g. corticosteroids, immunoglobulins). REVOLADE may be considered as second line treatment for adult non-splenectomized patients where surgery is contraindicated,
- To increase platelet counts in thrombocytopenic patients with chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon-based therapy, and
- For the treatment of adult patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

A systematic analysis of the different trials in the clinical database (across the entire REVOLADE development program) and the post-marketing safety database was conducted by Novartis Pharmaceuticals Canada Inc. to identify cases fulfilling Hy's Law criteria for drug-induced liver injury.

Based on this review, two (2) cases fulfilling Hy's law criteria were identified in adult cITP patients; three (3) further cases were identified in patients

treated for other, non-approved indications. The elevation of laboratory values typically occurred within three (3) months of initiation; in all five (5) cases the event resolved following REVOLADE discontinuation. In clinical trials in patients with chronic HCV infection, 11 patients treated with REVOLADE (1%) experienced drug-induced liver injury.

The Canadian Product Monograph for REVOLADE has been updated to reflect the risk of severe hepatotoxicity (i.e., severe hepatotoxicity and potentially fatal liver injury) in the existing Hepatotoxicity section under the Warnings and Precautions and to add an adverse drug reaction to the Adverse Reactions section.

In addition, an upper limit on the extent of alanine aminotransferase (ALT) elevation in patients with elevated ALT at baseline was added, to prohibit continuation of REVOLADE in patients with pre-existing hepatic disease, and in line with discontinuation criteria in the pivotal trials conducted in the approved indications.

Healthcare professionals should measure serum ALT, aspartate aminotransferase (AST) and bilirubin prior to initiation of REVOLADE, every 2 weeks during the dose adjustment phase, and then monthly following establishment of a stable dose. Healthcare professionals should discontinue REVOLADE if ALT levels:

- increase greater than or equal to 3x upper limit of normal (ULN) in patients with normal liver function or;
- increase greater than or equal to 3x baseline or greater than 5x ULN, whichever is the lower, in patients with elevations in transaminases before treatment and that are:
  - ◊ progressive, or
  - ◊ persistent for greater than or equal to 4 weeks, or
  - ◊ accompanied by increased direct bilirubin, or
  - ◊ accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

In Hong Kong, there are 4 registered pharmaceutical products containing eltrombopag, namely Revolade Tab 25mg (HK-60349), Revolade Tab 50mg (HK-60350), Revolade Tablets 25mg (Spain) (HK-62055) and Revolade Tablets 50mg (Spain) (HK-62056), which are registered by Novartis Pharmaceuticals (HK) Limited, and are prescription only medicines. As on 1 November 2016, DH has received two ADR cases in connection with eltrombopag but they are not related to severe hepatotoxicity. In view of the Health Canada's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on the above findings on 26 August 2016. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board and DH will remain vigilant on the safety updates on the products from other overseas drug regulatory authorities.

US: Opioid pain or cough medicines combined with Benzodiazepines: FDA requiring Boxed Warning about serious risks and death

On 31 August 2016, the US (United States) FDA (Food & Drug Administration) review has found that the growing combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. Opioids are used to treat pain and cough; benzodiazepines are used to treat anxiety, insomnia, and seizures. In an effort to decrease the use of opioids and benzodiazepines, or opioids and other CNS depressants, together, FDA is adding Boxed Warnings, their strongest warnings, to the drug labeling of prescription opioid pain and prescription opioid cough medicines, and benzodiazepines. Prescription opioid pain and cough medicines in US include alfentanil, buprenorphine, butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, remifentanil, sufentanil, tapentadol and tramadol. Benzodiazepines in US includes alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, oxazepam, quazepam, temazepam and triazolam. Other CNS depressants includes other sleep drugs and tranquilizers such as butabarbital sodium, eszopiclone, pentobarbital, ramelteon, secobarbital sodium, suvorexant, zaleplon and zolpidem; muscle relaxants such as baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine,

dantrolene, metaxalone, methocarbamol, orphenadrine and tizanidine; antipsychotics such as aripiprazole, asenapine, cariprazine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, molindone, olanzapine, paliperidone, perphenazine, pimavanserin, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine and ziprasidone.

FDA conducted and reviewed several studies showing that serious risks are associated with the combined use of opioids and benzodiazepines, other drugs that depress the CNS, or alcohol. Based on these data, FDA is requiring several changes to reflect these risks in the opioid and benzodiazepine labeling, and new or revised patient Medication Guides. These changes include the new Boxed Warnings and revisions to the Warnings and Precautions, Drug Interactions, and Patient Counseling Information sections of the labeling.

FDA is continuing to evaluate the evidence regarding combined use of benzodiazepines or other CNS depressants with medication-assisted therapy (MAT) drugs used to treat opioid addiction and dependence. FDA is also evaluating whether labeling changes are needed for other CNS depressants, and will update the public when more information is available.

Opioids are powerful prescription medicines that can help manage pain when other treatments and medicines cannot be taken or are not able to provide enough pain relief. Benzodiazepines are a class of medicines that are widely used to treat conditions including anxiety, insomnia, and seizures.

Health care professionals should limit prescribing opioid pain medicines with benzodiazepines or other CNS depressants only to patients for whom alternative treatment options are inadequate. If these medicines are prescribed together, limit the dosages and duration of each drug to the minimum possible while achieving the desired clinical effect. Warn patients and caregivers about the risks of slowed or difficult breathing and/or sedation, and the associated signs and symptoms. Avoid prescribing prescription opioid cough medicines for patients taking benzodiazepines or other CNS depressants, including alcohol.

Patients taking opioids with benzodiazepines, other CNS depressant medicines, or alcohol, and caregivers of these patients, should seek medical attention immediately if they or someone they are caring for experiences symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness.

In Hong Kong, there are 456 registered pharmaceutical products which contain the opioid pain or cough medicines listed in the FDA website, including: alfentanil (1 product), buprenorphine (8), codeine (319), dihydrocodeine (10), fentanyl (11), methadone (5), morphine (24), oxycodone (13), remifentanil (6), sufentanil (2), tapentadol (8) and tramadol (49); while there are no registered products which contain butorphanol, hydrocodone, hydromorphone, meperidine, oxymorphone or pentazocine. Besides, there are 89 registered products which contain the benzodiazepines listed in the FDA website, including: alprazolam (17), chlordiazepoxide (10), clobazam (1), clonazepam (10), clorazepate (1), diazepam (32), flurazepam (2), lorazepam (15) and triazolam (1); while there are no registered products which contain estazolam, oxazepam, quazepam and temazepam. As on 1 November 2016, DH has received one ADR case in connection with the concomitant use of opioid medicine and benzodiazepine.

CNS-related serious adverse effects, including slowed or difficult breathing and/ or sedation, are well-established adverse effects of opioid medicines and benzodiazepines which are documented in reputable drug references such as Martindale: the Complete Drug Reference. In view of the above FDA announcement, DH issued a letter to local healthcare professionals to reinforce the above risks on 1 September 2016. DH will remain vigilant on any safety update on opioid medicines and benzodiazepines from other overseas drug regulatory authorities.

DH endorsed batch recall of Cinotec Cream 0.005% (HK-40871) and 0.0125% (HK-40873)

On 3 August 2016, DH endorsed a licensed pharmaceutical manufacturer, Medipharma Ltd, to recall a total of five batches of Cinotec Cream 0.005% and 0.0125% from the market due to quality issue. The affected batches of Cinotec Cream 0.005% (HK-40871) are 602061, 509644, 502027; and the affected batches of Cinotec Cream 0.0125% (HK-40873) are 504190 and 509640.

Based on intelligence, samples from various batches of Cinotec Cream 0.005% and 0.0125% were collected for analysis. Upon testing by Government Laboratory, samples of the above five batches were found to have lower than the labelled claim of the active ingredient. Therefore, Medipharma recalled the above five batches of products from the market and the causes of the quality issue are under investigation.

Cinotec Cream contains fluocinolone acetonide which is a Part 1 poison, and is a prescription medicine for the treatment of eczema and allergic skin disorders. According to Medipharma, the above batches were supplied to Hospital Authority, DH clinics, private doctors and local pharmacies.

As on 1 November 2016, DH has not received any ADR report in connection with the above products. A notice was published on the website of Drug Office on 3 August 2016 to alert the public of the above product recall.

DH endorsed batch recall of eye drops labelled as Optomycin Eye Drops 0.5% (HK-49683) on the outer box with the batch number SL1515

On 19 August 2016, DH endorsed a licensed drug wholesaler, Ashford Pharmaceuticals Limited (Ashford), to recall from consumers a batch of eye drops labelled as Optomycin Eye Drops 0.5% (HK-49683) on the outer box with the batch number SL1515 due to a packaging error.

DH was notified by Ashford of a complaint from its client that some boxes of the above product had been found to contain another registered product called Optomycin-D Eye Drops (HK-49650). Preliminary investigations revealed that batch SL1515 is a unique batch number of Optomycin-D Eye Drops. However, some outer boxes intended for Optomycin Eye Drops 0.5% were wrongly printed with that batch number of Optomycin-D Eye Drops and packed with Optomycin-D Eye Drops. The bottles of these eye drops were correctly labelled as Optomycin-D Eye Drops.

So far, no evidence has indicated that other batches of the two eye drops were affected. DH has instructed Ashford to provide a detailed investigation report as soon as possible.

Optomycin Eye Drops 0.5%, containing chloramphenicol, is indicated for eye infections, while Optomycin-D Eye Drops contains a steroid, dexamethasone, apart from chloramphenicol. According to Ashford, the affected batch may have been supplied to Hospital Authority, private hospitals, private doctors and local pharmacies.

Members of the public using the two eye drops products should take extra caution to check if the bottle label of the eye drops matches with the box label and the prescriber's label. They should consult healthcare providers if in doubt.

A notice was published on the website of Drug Office on 19 August 2016 to alert the public of the above product recall.

DH endorsed batch recall of 70% Dextrose Injection, Partial Fill, 500mL/1000mL

On 29 August 2016, DH endorsed a licensed drug wholesaler, Vantone Medical Supplies Co., Ltd. (Vantone), to recall a batch of 70% Dextrose Injection, Partial Fill, 500mL/1000mL, because of a potential quality issue. The batch under recall is 48-010-JT.

DH has received notification from Vantone that the manufacturer in U.S. is recalling the above batch of product because of the potential contamination with an aromatic hydrocarbon resin. Assessments by the manufacturer indicated that the risk associated with the quality issue is negligible and the recall is a

Drug Recall

precautionary measure. So far, there is no evidence indicating that other batches are affected.

The above product is not registered in Hong Kong. However, according to Vantone, 72 bags of the affected product had been imported and supplied to Hospital Authority for the treatment of particular patients.

As on 1 November 2016, DH has not received any ADR report in connection with the concerned product. A notice was published on the website of Drug Office on 29 August 2016 to alert the public of the above product recall.

DH endorsed batch recall of Lescol Capsules 20mg (HK-44854)

On 29 August 2016, DH endorsed a licensed drug wholesaler, Novartis Pharmaceuticals (HK) Limited (Novartis), to recall one batch of Lescol Capsules 20mg (HK-44854) (Batch no.: B2014), due to quality issue.

DH received notification from Novartis that, during an ongoing stability study of the above product, the manufacturer in Spain found that samples of the above batch have failed one of the degradation product tests. Preliminary investigation revealed that the problem was due to exposure to light and heat for the particular batch during production. Assessments by the manufacturer indicated that the risk associated is minimal and the recall is a precautionary measure.

According to Norvartis, about 4,000 boxes containing 28 capsules per box of the affected product had been supplied to Hospital Authority, community pharmacies and private doctors.

Lescol Capsules containing fluvastatin is a prescription medicine used for the treatment of hyperlipidemia.

As on 1 November 2016, DH has not received any ADR report in connection with the concerned product. A notice was published on the website of Drug Office on 29 August 2016 to alert the public of the above product recall.

Drug Incident

Public urged not to buy or consume product with undeclared and controlled ingredient

On 11 August 2016, DH urged the public not to buy or consume a product named as Edpeptide 紅寶石 1 HR as it was found to contain an undeclared and controlled ingredient.

Acting on intelligence, DH purchased the above product for analysis. Test results of Government Laboratory on 11 August 2016 confirmed that the sample contained aminotadalafil, an analogue of a virility drug ingredient tadalafil.

Tadalafil is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138). It is a virility drug which should only be used under the advice of a doctor. Side effects of tadalafil include low blood pressure, headache, vomiting, dizziness and transient vision disturbances. It may interact with some drugs (such as nitroglycerin for treatment of angina) and cause decrease in blood pressure to dangerous levels. Improper use of tadalail may pose serious health risks, especially for patients with heart problems. Aminotadalafil, being chemically similar to tadalafil, is expected to pose similar health risks. Aminotadalafil is also a Part 1 poison.

A notice was published on the website of Drug Office on 11 August 2016 to alert the public of the above incident.

Public urged not to buy or consume product with undeclared and controlled ingredient

On 31 August 2016, DH urged the public not to buy or consume a product called ALLMAX RAPIDCUTS SHREDDED, as it was found to contain an undeclared and controlled ingredient.

Acting on intelligence, DH collected the above product for analysis. Test results of Government Laboratory confirmed that the sample contained

yohimbine.

Yohimbine is a Part 1 poison and has an antidiuretic effect. Its side-effects include elevation of heart rate and blood pressure, anxiety, manic reactions and bronchospasm. Products containing yohimbine can only be sold in a registered pharmacy under the supervision of a registered pharmacist.

A notice was published on the website of Drug Office on 11 August 2016 to alert the public of the above incident.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap 137) and the maximum penalty is a $30,000 fine and one year's imprisonment for each offence.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

Useful Contact

Drug Complaint:

Tel: 2572 2068

Fax: 3904 1224

E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920

Fax: 2319 6319

E-mail: adr@dh.gov.hk

Link: http://www.drugoffice.gov.hk/adr.html

Post: ***Pharmacovigilance Unit,***
Drug Office, Department of Health,
Rm 1856, 18/F, Wu Chung House,
213 Queen's Road East,
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The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.